The physician's role and responsibility in reporting adverse drug events in children

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How many children will experience hepatic toxicity, fatal or near-fatal cardiac rhythm disturbances, or other serious drug-related adverse events this year? The prevention of these adverse drug reactions (ADRs) is highly dependent on communication from health care professionals to Health Canada, and on Health Canada's ability to assess and communicate emerging information on drug risk to the public and its caregivers.

Postmarket surveillance of drug safety and therapeutic effectiveness in paediatrics is challenging because of under-reporting of adverse events (adverse drug reactions and medication incidents) as well as the level of off-label drug use, which is estimated at 70% to 80% of drugs used in children (1-4). Under-reporting of adverse events by health care professionals in general is an international reality (5,6). The extent of the problem of under-reporting of adverse events in paediatrics in Canada is not known. In 2001, 8123 domestic adverse events in all age categories were reported to Health Canada's Canadian Adverse Reaction Monitoring Programme. This is compared with an excess of 350,000 total domestic and foreign adverse events reported in the United States on an annual basis. In 2001, Canadian pharmacists reported over 28% of total cases and physicians reported 25.5% (7). In addition, over 81,000 international reports were submitted. For the years 1998 to 2000, between 4.2% and 5.0% of Canadian adverse event reports involved children younger than the age of 18 years (8). It is not possible to determine how many of these reports are from paediatricians or family physicians that prescribe for children. In paediatrics, where fewer therapeutic agents have been the subject of rigorous clinical trials leading to a reliable basis for approved indications by Health Canada or other national regulators, there is the need for enhanced vigilance and reporting to a central database. When spontaneous ADR reporting databases have been examined for evidence of paediatric ADR reports, there is clear evidence that ADRs, often serious in nature, occur in children. Given the absence of a formal premarket evidence base for dosage, frequency and special concerns for differences in childhood drug metabolism and interactions, aggressive pharmacovigilance and reporting of suspected ADRs in children should be considered a responsibility for every physician prescribing for children as well as for pharmacists, nurses, and other health professionals who provide advice and follow-up to children who are receiving medications.

Drug approvals are based on behaviour of the product in sample populations in clinical trials, few of which include children. Prescribing practice engages the practitioner in interpreting these general results from clinical trials to the special needs of a single patient, often referred to as the 'art' of medicine. In the absence of reliable information from childhood population sampling within a clinical trial, the responsibility of the practitioner of paediatric prescribing becomes further challenged in providing the correct choice of therapeutic agent, dose, route and pharmaceutical form of the product. 'N of one' trials are often the result and outcomes of these clinical experiences are important. While reports of therapeutic benefits would contribute to the understanding of appropriate use of prescription drugs in children, unsatisfactory outcomes and, most emphatically, adverse reaction reports need to be regarded as the professional duty of a responsible physician.

Reasons for inadequate premarket experience in children is not the topic of this article, but reasons vary from lack of commercial interest in the industry sector, to absent or controversial ethical guidance to researchers as to the appropriateness of including pediatric subjects in clinical trials of new active substances. The recent publication of the ICH E-11 Guidance titled *Clinical Investigation of Medicinal Products in the Pediatric Population* (9) and upcoming revision of Tri-Council Policy should, hopefully, clarify these issues. However, special care will always be required in selecting children as subjects in clinical trials for new active substances because there are high failure rates in phase 2 trials, as well as surprising failures in phase 3 trials, both based on failure to demonstrate efficacy, as well as for substantial safety concerns. Nevertheless, there are increasing incentives to industry to work within these special considerations and for clinical trialists to include paediatric studies in drug development programs where the product is likely to provide benefits to childhood conditions or diseases. Recently, financial incentives in the United States have led to the increased evaluation of dosage, dosage frequency and pharmacokinetics in children. These studies are not powered for safety and, consequently, postmarket reporting of ADRs remains the sole source of safety information.

Reasons for inadequate reporting of paediatric postmarket experience most likely resides squarely in the realm of inconvenience for the busy practitioner, although failure on the part of the practitioner to distinguish adverse events from disease or other process may also be a factor.

This leads one to conclude that there is a need for Health Canada to facilitate reporting of adverse events in children. Also, consideration must be given to a more active process in monitoring all postmarket experience for new drugs that may

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have received limited or no premarket evaluation in paediatric age groups. A study on serious and life-threatening ADRs in children newborn to 18 years of age, funded by Health Canada, is under discussion with the Canadian Paediatric Surveillance Program. The study will enable Health Canada to understand better the scope of the ADR problem in paediatric patients and, in addition, will help to determine the feasibility of active surveillance as a user-friendly tool for identifying serious and life-threatening ADRs in children. The study will be launched in 2003. Active surveillance is a criteria-based audit of drug use, which involves the reporting of experiences, including normal outcomes in addition to adverse experiences. In this manner, while less efficient than active or placebo controlled trials, one can gather real-life safety data in addition to outcome measurement. Active surveillance of paediatric 'drugs of choice', which lack specific labelled indications for appropriate age groups, is a further option to be considered.

Lastly, the present system of passive reporting of ADRs in children needs to be taken seriously. It forms the basis for comparison of Canadian experience to that reported internationally and creates the 'signals' needed for postmarket identification of potential problems. Passive reporting is health care provider- or patient-initiated and lacks the structure of a clinical trial or an active surveillance program. Nevertheless, it is a serious tool to identify difficulties that may exist in childhood drug use.

Reports of all regulatory and safety updates on therapeutic health products that are licensed for the Canadian market initiated either by Health Canada or manufacturers can be received through automatic e-mail messaging by enrolling in the Health Products and Food Branch list-server at www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/cadrnwsletter.html.

Reporting of adverse events in children can be done with a toll-free telephone call to 866-234-2345, or toll-free fax 866-678-6789 by completing and faxing or mailing the form located at www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf or by completing the ADR form found in the Appendix of the *Compendium of Pharmaceuticals and Specialties* (10).

Health care providers who prescribe for children have a professional responsibility to report even suspected adverse drug experiences in children. It is time to take this responsibility more seriously.

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